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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/613,006	07/10/2000	Mark A. Schena	M-9216 US	9156

7590 03/04/2003

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EXAMINER
FORMAN, BETTY J

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/613,006	SCHENA, MARK A.	
	Examiner	Art Unit	
	BJ Forman	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *19 22* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

FINAL ACTION

1. This action is in response to papers filed 15 August 2002 in Paper No.22; papers filed 13 December 2002 in Paper No. 23; and papers filed 27 January 2003 in Paper No. 24. Amendments filed with Paper No. 22 amended the specification to identify nucleic acid sequences by SEQ ID NO: and to supplement the gene names abbreviated and discussed on page 17. Amendments of Paper No. 22 also canceled claims 1-27 and added claims 28-45. Amendments of Paper No. 23 amended Claim 28 and added Claim 46. A Declaration filed under 36 C.F.R. 1.132 was also submitted with Paper No. 23 along with paper and computer readable copies of the sequence listing. Paper No. 24 contained the resume of Neil Winegarden, as a supplement to the Declaration of Paper No. 23.

All of the amendments and papers have been thoroughly reviewed and entered. The previous rejections in the Office Action of Paper No. 18 dated 15 May 2002 are withdrawn in view of the amendments. All of the arguments have been thoroughly reviewed but are deemed moot in view of the amendments, withdrawn rejections and new grounds for rejection.

New grounds for rejection are discussed.

Claims 28-46 are under prosecution.

Information Disclosure Statement

2. The references listed on the 1449 received 25 June 2002 and 15 August 2002 have been reviewed and considered. Copies of the signed 1449s are enclosed with this action.

Claim Rejections - 35 USC § 112

35 U.S.C. 112: second paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 28-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 28-46 are indefinite in Claim 28 because the claim is drawn to a method of simultaneously genotyping multiple samples comprising incubating a microarray of samples from multiple individuals. The final method step detects hybrids wherein a hybrid is indicative of a genotype of **a** mammal. First, the claim is indefinite because the relationship between the multiple individuals and the mammal of step (2) is undefined. Second, the claim is indefinite because it is unclear whether genotyping of multiple samples is accomplished as claimed because the method does not recite steps for genotyping multiple samples. Finally, the claim is indefinite because it is unclear whether and/or how simultaneous genotyping accomplished as claimed because the method steps do not recite simultaneous detection and/or genotyping. It is suggested that Claim 28 be amended to clarify.

b. Claims 28-46 are further indefinite in Claim 28 (d) for the recitation "the array" because the recitation lacks proper antecedent basis in the "microarray" of step 1. It is suggested that Claim 28 be amended to provide proper antecedent basis.

c. Claims 31 and 44 are each indefinite for the recitation "the plurality of classes of polynucleotides" because the recitation lacks proper antecedent basis in the "polynucleotide samples" and "plurality of samples" recited in Claim 28. It is suggested that Claims 31 and 44 be amended to provide proper antecedent basis.

d. Claim 36 is indefinite for the recitation "the mixture of oligonucleotides" because the recitation lacks proper antecedent basis in the "probe mixture of Claim 28. It is suggested that Claim 36 be amended to provide proper antecedent basis.

Declaration under 37 CFR 1.132

5. The Declaration under 37 CFR 1.132 filed 13 December 2002 sufficiently provides evidence that the specification support the newly claimed "single round of hybridization".

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 28-33, 35, 37-44 and 46 are rejected under 35 U.S.C. 102(e) as being anticipated by Fan et al (U.S. Patent No. 2002/0001801 A1, filed 16 February 2000).

Regarding Claim 28, Fan et al disclose a method of simultaneously genotyping multiple samples in a single round of hybridization comprising: incubating a microarray of polynucleotide samples from multiples individuals with a probe mixture of oligonucleotides of known sequence wherein the microarray contains a plurality of samples containing genotypes of interest with each sample in a distinct location (i.e. on a bead,¶ 22) each sample has polynucleotides with a defined segment containing a marker selected from a marker for a gene and markers for one or more allelic variants of the gene, the oligonucleotides in the probe mixture consist essentially of oligonucleotides of known sequence and length and having sequences specifically complementary to those within the defined segments for each sample for which the genotype is to be determined wherein the oligonucleotides complementary to the polynucleotides are selected form those with sequences complementary to a segment containing the marker for a gene, one or more allelic variants of the gene and the gene and one or more allelic variants of the gene the incubating forms hybrids of polynucleotides of the array and complementary oligonucleotides and allows discrimination at a single nucleotide resolution and detecting stable hybrids formed during the incubation wherein the formation of a hybrid after a single round of hybridization is indicative of a genotype (¶ 22-33, 133-148 and Claim 23).

Regarding Claim 29, Fan et al disclose the method wherein the polynucleotide samples of the microarray are amplification products (¶ 26 and 32).

Regarding Claim 30, Fan et al disclose the method wherein the amplification products are produced by a PCR method (¶ 26 and 32).

Regarding Claim 31, Fan et al disclose the method wherein the plurality of sample is at least 10 (¶ 22 and 36).

Regarding Claim 32, Fan et al disclose the method wherein an allele is associated with a disease (¶ 6, 22-23 and 133).

Regarding Claim 33, Fan et al disclose the method wherein the disease is a human disease (¶ 6, 22-23 and 133).

Regarding Claim 35, Fan et al disclose the method wherein the microarray is on a surface containing at least 1000 locations/cm^2 (¶ 36).

Regarding Claim 37, Fan et al disclose the method wherein the oligonucleotides in the mixture are between about 10 and 30 nucleotides in length (¶ 81).

Regarding Claim 38, Fan et al disclose the method wherein the distinct segment is between about 40 and 1000 nucleotides (¶ 56).

Regarding Claim 39, Fan et al disclose the method wherein incubating is in an aqueous solution comprising salts and detergent (see hybridization buffer w/ SSC and Tween 20,¶ 238).

Regarding Claim 40, Fan et al disclose the method wherein hybridization is performed at a temperature about 10° C below melting of stable hybrids (¶ 148).

Regarding Claim 41, Fan et al disclose the method wherein the oligonucleotides of known sequence are labeled (¶ 137-138).

Regarding Claim 42, Fan et al disclose the method wherein the label is fluorescent (¶ 138).

Regarding Claim 43, Fan et al disclose the method wherein samples from homozygotes and heterzygotes are distinguishable (¶ 6 and 127).

Regarding Claim 44, Fan et al disclose the method wherein the plurality of samples is at least 5,000 (¶ 34 and 36).

Regarding Claim 46, Fan et al disclose the method wherein the mammal is human (¶ 22-26).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 28-39 and 41-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Drmanac (U.S. Patent No. 6,025,136, filed 28 August 1997) in view of Brown et al (U.S. Patent No. 5,807,522, filed 7 June 1995).

Regarding Claim 28, Drmanac teaches a method of simultaneously genotyping multiple samples comprising: incubating a microarray of polynucleotide samples from multiple individuals with probes of a known sequence wherein the array contains a plurality of sample containing genotypes of interest with each sample in a distinct location each sample has polynucleotides with a defined segment containing a marker selected from a gene or markers for one or more allelic variants of the gene, the probes consist essentially of oligonucleotides of known sequence and length and having sequences specifically complementary to those within the defined segments for each sample for which a genotype is to be determined wherein the oligonucleotides are selected from those complementary to the gene and/or one or more allelic variants of the gene, the incubating form hybrids of arrayed polynucleotides and complementary oligonucleotides and allows discrimination at a single nucleotide resolution and detecting stable hybrids form during the incubation wherein hybrid formation is indicative of a genotype (Example 3, Column 5, line 37-Column 6, line 3 and Example 6, Column 7, line 25-Column 8, line 46). Drmanac teaches the method comprising multiple rounds of hybridization wherein e.g. a round hybridizes with positive probes and a subsequence round hybridizes with negative probes (Column 7,lines 30-61) but Drmanac does not teach detection of the hybrid following a single round of hybridization is indicative of a genotype. However, genotyping

comprising a single round of hybridization was well known in the art at the time the claimed invention was made as taught by Brown et al. Brown et al. teach a similar method of simultaneously genotyping multiple samples comprising: incubating a microarray of polynucleotide samples from multiple individuals with a probe mixture wherein the microarray contains a plurality of samples containing genotypes of interest (amplified region of interest), each sample had polynucleotides with a defined segment containing a marker (region of interest) and the probes consist of oligonucleotides complementary to the regions of interest, the incubating form hybrids and allows discrimination at a single nucleotide resolution (i.e. perfect match) and detecting stable hybrids following a single round of hybridization which is indicative of genotype (Column 15, lines 19-52). Brown et al further teach that their method wherein differentially labeled probes detected following a single hybridization permits simultaneous detection of the plurality of samples with "significant time and cost savings" (Column 15, lines 13-16, 39-43 and 52-67). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the differentially labeled probes of Brown et al to the method of Drmanac and to differentially label their marker-specific probes to thereby permit simultaneous detection of multiple samples following a single hybridization step for the expected benefits of significantly saving time and money as taught by Brown et al (Column 15, lines 13-16, 39-43 and 52-67).

Regarding Claim 29, Drmanac teaches the method wherein the samples are amplification products (Column 5, lines 30-35).

Regarding Claim 30, Drmanac teaches the method wherein the amplification products are produced by PCR (Column 5, lines 30-35).

Regarding Claim 31, Drmanac teaches the method wherein the plurality of samples is at least 10 i.e. a subarray contains a sample from each of 64 patients (Column 5, lines 59-60).

Regarding Claim 32, Drmanac teaches the method wherein an allele of the gene is associated with a disease (Column 2, lines 5-12 and Examples 6-8, Column 7, line 25-Column 10, line 21).

Regarding Claim 33, Drmanac teaches the method wherein the disease is human disease (Column 2, lines 5-12 and Examples 6-8, Column 7, line 25-Column 10, line 21).

Regarding Claim 34, Drmanac teaches the method wherein the samples are diagnostically important (Column 2, lines 7-12) but they do not teach specific genetic loci. However, It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the genetic diagnostic microarrays of Drmanac to provide specific genetic loci e.g. β-globin, CFTR and GALT, to thereby provide microarrays for disease-specific diagnosis for the expected benefit of rapid diagnosis of clinically important diseases as taught by Brown et al. (Column 15, lines 59-67).

Regarding Claim 35, Drmanac teaches the method wherein the microarray is on a surface comprising at least 1000 locations/cm^2 i.e. 25/mm^2 (Column 5, lines 46-48).

Regarding Claim 36, Drmanac teaches the method wherein the mixture of oligonucleotides comprises at least 10 different sequences i.e. 5 positive for one allele, 5 for another allele and 2 negative (Column 7, lines 29-33).

Regarding Claim 37, Drmanac teaches the method wherein the oligonucleotides are between about 10 and 30 nucleotides in length (Column 4, line 59-Column 5, line 4).

Regarding Claim 38, Drmanac teaches the method wherein the distinct segment is between about 40 and about 1000 nucleotides in length (Column3, lines 27-34).

Regarding Claim 39, Drmanac teaches the method wherein the incubating is in an aqueous solution comprising salt and detergent (Column 18, lines 17-30).

Regarding Claim 41, Drmanac teaches the method wherein the oligonucleotides are labeled (Column 5, lines 5-13).

Regarding Claim 42, Drmanac teaches the method wherein the label is fluorescent (Column 5, lines 5-13).

Regarding Claim 43, Drmanac teaches the method wherein samples from homozygotes and heterozygotes are distinguishable (Column 4, lines 7-19).

Regarding Claim 44, Drmanac teaches the method wherein the plurality of samples is at least 5000 i.e. a subarray contains 256 samples (Column 4, lines 42-43) and the array comprises 50 subarrays (Column 3, lines 33-36).

Regarding Claim 45, Drmanac teaches a method of simultaneously genotyping multiple samples (Example 6, Column 7, line 25-Column 8, line 46) wherein the samples are diagnostically important (Column 2, lines 7-12) but they do not teach the samples are neonatal blood samples. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the diagnostic array comprising mutated genes as taught by Drmanac to comprise multiple forms of genes from neonatal blood samples for the obvious benefits of prenatal diagnosis i.e. by detecting the presence of mutant genes in neonatal samples, the disease maybe prevented and/or treated as early as possible.

Regarding Claim 46, Drmanac teaches the method wherein the mammal is a human (Column 8, lines 52-62).

10. Claim 40 is rejected under 35 U.S.C. 103(a) as being unpatentable over Drmanac (U.S. Patent No. 6,025,136, filed 28 August 1997) in view of Brown et al (U.S. Patent No. 5,807,522, filed 7 June 1995) as applied to Claim 28 above and further in view of Hames et al (Nucleic Acid Hybridization: a practical approach, IRL Press, Washington DC, 1985, pages 105-108).

Regarding Claim 40, Drmanac teaches a method of simultaneously genotyping multiple samples comprising: incubating a microarray of polynucleotide samples from multiple individuals with probes of a known sequence wherein the array contains a plurality of sample (Column 7, line 25-Column 10, line 21) and Brown et al teach the similar method wherein stable hybrids are detected following a single round of hybridization and the detection is indicative of genotype (Column 15, lines 19-52). Drmanac and Brown et al are silent regarding hybridizing at about 10° C below stable hybrid melting temperature. However it was well known in the art at the time the claimed invention was made that stable hybrids of closely related sequences are hybridized and distinguishable at about 10° C below melting temperature as taught by Hames et al (page 105 (i) and page 108, first full paragraph, lines 8-10). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the hybridization temperatures taught by Hames et al (i.e. about 10° C below melting) to the allele-specific hybridizations of Drmanac and Brown et al because their hybridizations are designed to distinguish between closely related sequences. Therefore, one of ordinary skill in the art would have been motivated to hybridize the nucleic acids of Drmanac and Brown et al at about 10° C below melting for the obvious benefits of distinguishing between their closely related sequences as taught by Hames et al and to thereby accurately genotype the individuals.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:30 TO 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

BJ Forman, Ph.D.
Patent Examiner
Art Unit: 1634
February 27, 2003